REMARKS

Reconsideration is requested.

The claims have been amended, without prejudice, to advance prosecution.

Claim 17 has been added and finds support, for example, on page 13 of the specification. No new matter has been added.

The Section 112, first paragraph "written description", rejection of claims 1, 4, 5, 6, 9 and 10 is traversed.

Initially, the applicants note that claims 2, 3, 7, 8 and 11-15, which were not rejected as allegedly being indefinite, include as embodiments fragments and variants which were apparently the basis of the Section 112, first paragraph, rejection of claims 1, 4, 5, 6, 9 and 10.

As for the rejected claims and the Examiner's comments regarding the recited fragments and variants, consideration of the following and the attached is requested.

A U.S. patent application need not and preferably does not include that which is known. Moreover, examples are not necessary to support the adequacy of a written description, the written description standard may be met even where actual reduction to practice of an invention is absent; and there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure. See Falkner v. Inglis, Fed. Cir. 05-1324, May 26, 2006.

The Falkner court explained that

> "a claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person

> comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation."

Moreover, the Falkner court explained that there is no per se rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art. See Capon v. Eshhar 418 F.3d at 1357 ("None of the cases to which the Board attributes the requirement of total DNA re-analysis, i.e.. Regents V. Lilly, Fiers v. Revel, Amgen or Enzo Biochem require a re-description of what was already known."). Thus, the Falkner court found that when the prior art includes nucleotide information, for example, precedent does not set a per se rule that the information must be determined afresh.

Rather,

> "The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science." Falkner at 17.

The Falkner court further explained that a requirement that applicants recite known structures or sequences, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee

and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention.

The Examiner is urged to appreciate that the sequences of human and bovine α-lactalbumin were known at the time of the present invention. A copy of the 123 amino acid sequences is attached for the Examiner's convenience.

The Examiner is understood to have rejected claims 1, 4, 5, 6, 9 and 10 for allegedly not being supported by an adequate written description in the recitation of a fragment of α-lactalbumin.

The claimed fragments comprise a region of α-lactalbumin corresponding to the region of α-lactalbumin which forms the interface between the alpha and beta domains, which the applicants have discovered to be important to obtain the biological activity of the claimed complexes. The specification further describes the claimed fragments in ¶¶[0022]-[0023] of the U.S. Patent Office published version of the application (Patent Application Publication No. 2005/0085416 A1). The recited region which forms the interface between the alpha and beta domains is described in ¶[0033] of the published version of the application (i.e., defined by amino acids 34-38 and 82-86 for human α-lactalbumin) such that "suitable fragments will include these regions, and preferably the entire region from amino acid 34-86 of the native protein." See ¶[0033] of the published version of the application.

Moreover, the specification describes the required biological activity of the claimed complex at, for example, ¶[0019] of the published version of the application. Methods are described for testing fragments of the invention for the required biological

activity. The specification describes the claimed fragments to the extent required by the law relating to Section 112, first paragraph, such as is articulated by the Falkner court.

The Examiner is understood to have also rejected claims 1, 4, 5, 6, 9 and 10 for allegedly not being supported by an adequate written description in the recitation of a variant of α-lactalbumin.

The claimed variants of α-lactalbumin are described in ¶[0020] of the published version of the specification. The claims further require that the claimed complex containing a recited variant must be biologically active, as described in ¶[0019] of the published version of the specification. Preferred examples of the claimed variants are described, for example, in ¶¶[0024]-[0032] of the published version of the specification.

The specification describes the claimed variants to the extent required by the law relating to Section 112, first paragraph, such as is articulated by the Falkner court.

The Examiner is further understood to have rejected claims 1, 4, 5, 6, 9 and 10 for allegedly not being supported by an adequate written description in the recitation of a cofactor other than C:18:1:9 cis fatty acid. Specifically, the Examiner makes reference to "page 51" (see page 3 of the Office Action dated December 30, 2005) of the specification however the filed specification is believed to contain 42 pages such that the Examiner's reference is not understood. Clarification is requested in the event the rejection based on the noted recitation is maintained.

Contrary to the Examiner's suggestion, the specification describes cofactors of the claims at, for example, ¶[0046] of the published version of the specification. Moreover, the results of Figure 3, for example, demonstrates the C18:1:11 (vaccine or vaccenic acid) is a useful cofactor according to the claimed invention. The specification

further demonstrates C18:1:9 (oleic acid) as a cofactor of the invention. The Examiner is urged to appreciate that the proviso of claim 1 provides that when the complex comprises full length α-lactalbumin or a variant of α-lactalbumin in which the calcium binding site has been modified so that the affinity for calcium is reduced, or it is no longer functional, the cofactor is other than C18:1:9 cis fatty acid.

The specification is submitted to provide an adequate written description of the recited cofactor.

Finally, the Examiner's apparent requirement for a "SEQ ID NO:" to be provided in claim 9 to allegedly satisfy the written description requirement is submitted, with due respect, to not be required for at least the reasons described by the Falkner court and summarized above.

Withdrawal of the Section 112, first paragraph "written description", rejection of claims 1, 4, 5, 6, 9 and 10 is requested.

To the extent not obviated by the above amendments, the Section 1112, second paragraph, rejection of claims 1-15, is traversed. Consideration of the following in this regard is requested.

Claims 2 and 5 have been amended above to advance prosecution in response the Examiner's comments. The amendments have been made without prejudice.

As noted above, the specification provides a description of the recited region corresponding to the region of α-lactalbumin which forms the interface between the alpha and beta domains. The claims and specification are directed to one of ordinary skill in the art. The metes and bounds of the objected-to claim recitation will be understood by one of ordinary skill in the art in the absence of a "SEQ ID NO:".

The metes and bounds of the mutant of claims 12 will be appreciated form, for example, the disclosure of ¶[0034] of the published version of the specification. Nothing further should be required in this regard.

Finally, claim 15 has been revised to include a positive result of the treatment method. One of ordinary skill will appreciate however a number of methods available for administration, such as those described in the specification. Claim 17 has been added to further specific modes of administration.

Withdrawal of the Section 112, second paragraph, rejection of claims 1-15.

The Section 102 rejection of claims 1-6, 10, 11 and 13-15 over Swensson (PNAS (April 11, 2000), Vol. 97, No. 8, pp 4221-4226), is traversed. Reconsideration and withdrawal of the rejection are requested as the C18:1 fatty acid of the reference is specifically described as "oleic acid" on page 4222, right column, first full paragraph ("oleic acid (18:1)") which is, in fact, C18:1:9acid (see attached page 1221, column 2 of the Merck Index (Merck & Co., Inc., Whitehouse Station, NJ (2001)) and would not be "represented by C18:1:11", as asserted by the Examiner. See page 5 of the Office Action dated December 30, 2005. The C18:1:11 isomer is generally referred to as vaccine acid or vaccenic acid, as evidenced by the attached copy of page 1764 of the Merck Index.

As the reference fails to teach each and every aspect of the claimed invention, withdrawal of the Section 102 rejection is requested.

The Section 103 rejection of claims 1 and 6-8 over Swensson in view of Permyakov (Protein Engineering, Vol. 14, No. 10, pp 785-789, 2001), is traversed. Reconsideration and withdrawal of the rejection are requested as the secondary

reference fails to cure the above-noted deficiencies of the primary reference. Withdrawal of the rejection is requested.

For completeness, the applicants note that differences between the presently claimed invention and the primary reference include more than the Examiner-articulated "mutations of α-lactalbumin" (see page 7 of the Office Action dated December 30, 2005). Specifically, the primary reference does not teach or suggest the use of a cofactor of the present claims in conjunction with either native α-lactalbumin or a modified α-lactalbumin wherein the calcium binding site has been modified so that the affinity for calcium is reduced. There was no motivation in the cited art to have combined the references to have made the claimed invention. Moreover, even if motivation existed in the art to have combined the references, which it does not, the combination of a modified α-lactalbumin of the claims wherein the calcium binding site has been modified so that the affinity for calcium is reduced with the cofactor of the primary reference is believed to be excluded and there is no suggestion in the primary reference to use a cofactor other than C18:1:9 cis fatty acid.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

BJS:
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

THIRTEENTH EDITION

Editorial Staff

Maryadele J. O'Neil, *Senior Editor*
Ann Smith, *Senior Associate Editor*
Patricia E. Heckelman, *Associate Editor*

John R. Obenchain Jr., *Editorial Assistant*
Jo Ann R. Gallipeau, *Technical Assistant*
Mary Ann D'Arecca, *Administrative Associate*

Susan Budavari, *Editor Emeritus*

Published by
Merck Research Laboratories
Division of

MERCK & CO., INC.
Whitehouse Station, NJ

2001

Hydrochloride. [6696-47-5] $C_{35}H_{61}NO_{12}$.HCl. Long needles from ethyl acetate, mp 134-135°. $[\alpha]_D^{25}$ −54° (methanol). Freely sol in water. Forms various cryst hydrates. LD_{50} in mice, rats (mg/kg): 8200, >10000 orally; 600, 400 i.v. (Sous).

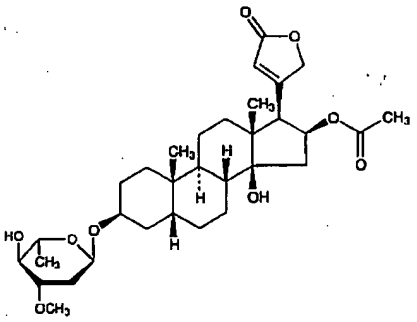
Phosphate. [7060-74-4] Matromycin. $C_{35}H_{61}NO_{12}.H_3PO_4$; mol wt 785.85.

Triacetyl deriv, *see* Troleandomycin

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antibacterial.

6896. Oleandrin. [465-16-7] (3β,5β,16β)-16-(Acetyloxy)-3-[(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)oxy]-14-hydroxycard-20(22)-enolide; neriolin; Corrigen; Folinerin. $C_{32}H_{46}O_9$; mol wt 576.72. C 66.64%, H 8.39%, O 24.97%. From the leaves of *Nerium oleander* L., *Apocynaceae* (Laurier rose): Tanret, *Compt. Rend.* **194**, 914 (1932); Neumann, *Ber.* **70**, 1547 (1937). Prepn by enzymic hydrolysis of purechitoxin: Hassall, *J. Chem. Soc.* **1951**, 3193. Structure: Tschesche, *Ber.* **70**, 1554 (1937); Krasso *et al., Helv. Chim. Acta* **46**, 1691 (1963).

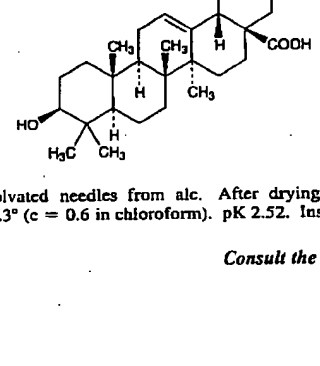


Crystals from dil methanol, mp 250°. $[\alpha]_D^{25}$ −48.0° (c = 1.3 in methanol). uv max: 220 nm (log ε 4.20). Practically insol in water. Sol in alcohol, chloroform.

Desacetyloleandrin. $C_{30}H_{46}O_8$. Leaflets from alcohol, mp 238-240°. $[\alpha]_D^{18}$ −24.9°.

THERAP CAT: Cardiotonic; diuretic.

6897. Oleanolic Acid. [508-02-1] (3β)-3-Hydroxyolean-12-en-28-oic acid; oleanol; caryophyllin. $C_{30}H_{48}O_3$; mol wt 456.70. C 78.90%, H 10.59%, O 10.51%. Occurs in the free state in leaves of *Olea europaea, Oleaceae,* in leaves of *Viscum album* L., *Loranthaceae,* in buds of *Syzygium aromaticum* (L.) Merr. & Perry, *Myrtaceae* (cloves), in *Swertia japonica* (Maxim.) Makino, and in *Centaurium umbellatum* Gilib. (*Erythraea centaurium* (L.) Pers.), *Gentianaceae;* as acetate in birch bark, as glycoside in many saponins. Isoln procedures (from cloves): Winterstein, Stein, *Z. Physiol. Chem.* **202**, 222 (1931); Ruzicka, Hofmann, *Helv. Chim. Acta* **19**, 114 (1936); Picard *et al., J. Chem. Soc.* **1939**, 1047. Structure: Ruzicka *et al., Helv. Chim. Acta* **29**, 210 (1946). *Review:* J. Simonsen, W. C. T. Ross, *The Terpenes* vol. 5 (University Press, Cambridge, 1957) pp 221-285. *Cf.* α- and β-amyrin.



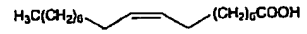
Fine, solvated needles from alc. After drying, mp 310°. $[\alpha]_D^{20}$ +83.3° (c = 0.6 in chloroform). pK 2.52. Insol in water. Sol in 65 parts ether, 106 parts 95% alcohol, 35 parts boiling 95% alcohol, 118 parts chloroform, 180 parts acetone, 235 parts methanol.

Acetate. $C_{32}H_{50}O_4$. Needles from methanol, mp 268°. $[\alpha]_D^{17}$ +74.5° (c = 0.6 in $CHCl_3$).

Methyl ester. $C_{31}H_{50}O_3$. mp 201°. $[\alpha]_D^{20}$ +75° (c = 0.6 in $CHCl_3$).

Acetate of methyl ester. $C_{33}H_{52}O_4$. Needles from alcohol, mp 223°. $[\alpha]_D^{20}$ +70° (c = 0.6 in $CHCl_3$).

6898. Oleic Acid. [112-80-1] (*Z*)-9-Octadecenoic acid. $C_{18}H_{34}O_2$; mol wt 282.46. C 76.54%, H 12.13%, O 11.33%. Obtained by the hydrolysis of various animal and vegetable fats and oils. Prepn from olive oil: *Biochem. Prepn.* **2**, 100 (1952). Separation from olive oil by double fractionation via urea adducts: Rubin, Paisley, *Biochem. Prepn.* **9**, 113 (1962). Stereochemistry: Thieme, *Ann.* **343**, 354 (1905). Synthesis: Robinson, Robinson, *J. Chem. Soc.* **127**, 175 (1925). ^{13}C-NMR studies: W. Stoffel *et al., Z. Physiol. Chem.* **353**, 1962 (1972); J. G. Batchelor *et al., J. Org. Chem.* **39**, 1698 (1974). Toxicity data: L. Orö, A. Wretlind, *Acta Pharmacol. Toxicol.* **18**, 141 (1961). Exptl use of ^{131}I-labelled oleic acid in myocardial imaging: F. J. Bonte *et al., Radiology* **108**, 195 (1973). Review of diagnostic use of ^{3}H-oleic acid in pancreatic function: N. T. Pedersen, *Digestion* **37**, Suppl. 1, 25-34 (1987).



Pure oleic acid is a colorless or nearly colorless liq (above 5-7°). d_{25}^{25} −0.895. Solidifies to cryst mass, mp 4°. bp_{100} 286°. At atm pressure it dec when heated at 80-100°. n_D^{18} 1.463; n_D^{26} 1.4585. Iodine no. 89.9; acid value 198.6. On exposure to air, especially when impure, it oxidizes and acquires a yellow to brown color and rancid odor. Practically insol in water. Sol in alcohol, benzene, chloroform, ether, fixed and volatile oils. *Keep well closed, protected from light.* LD_{50} i.v. in mice: 230±18 mg/kg (Orö, Wretlind). Several grades of the acid are available in commerce, varying in color from pale yellow to red-brown and, depending on the amount of saturated acid present, becoming turbid at 8-16°. The acid of commerce usually contains 7-12% saturated acids, e.g., stearic, palmitic; also some linoleic, etc., unsaturated acids.

Methyl ester. Methyl oleate. $C_{19}H_{36}O_2$. Prepd by refluxing oleic acid with *p*-toluene sulfonic acid in methanol: Rubin, Paisley, *loc. cit.* Iodine no. 85.6. d_4^{18} 0.879. n_D^{26} 1.4510. bp_2 168-170°. Miscible with anhydr ethanol, ether.

Ethyl ester. Ethyl oleate; (*Z*)-9-octadecenoic acid ethyl ester. $C_{20}H_{38}O_2$. Yellowish, oily liquid. d 0.87. bp 205-208° (some dec). Insol in water. Misc with alcohol, ether.

Barium salt. Barium oleate. $C_{36}H_{66}BaO_4$. Yellowish-white, granular masses. *Poisonous!* Practically insol in water. Slightly sol in boiling alcohol.

Sodium salt. [143-19-1] Eunatrol. $C_{18}H_{33}NaO_2$; mol wt 304.44. White powder, slight tallow-like odor. Sol in ~10 parts water, ~20 parts alcohol. Generally contains small quantities of the sodium salts of stearic, etc. acids. Alkaline in aq solns due to hydrolysis but not in alcohol solns.

Caution: Mildly irritating to skin, mucous membranes.

USE: Prepn of Turkey red oil, soft soap and other oleates; in polishing compds; waterproofing textiles, oiling wool; manuf driers; thickening lubricating oils. Pharmaceutic aid (solvent). The barium salt in rodent extermination.

THERAP CAT: Diagnostic aid (pancreatic function).

6899. Oleuropein. [32619-42-4] [2*S*-(2α,3*E*,4β)]-3-Ethylidene-2-(β-D-glucopyranosyloxy)-3,4-dihydro-5-(methoxycarbonyl)-2*H*-pyran-4-acetic acid 2-(3,4-dihydroxyphenyl)ethyl ester. $C_{25}H_{32}O_{13}$; mol wt 540.51. C 55.55%, H 5.97%, O 38.48%. Bitter glucoside; first *secoiridoid* to be isolated. Isolation from olives and the leaves and bark of the olive tree, *Olea europaea* L., *Oleaceae* and structural studies: Panizzi *et al., Gazz. Chim. Ital.* **90**, 1449 (1960); Beyerman *et al., Bull. Soc. Chim. France* **1961**, 1821; Shasha, Leibowitz, *J. Org. Chem.* **26**, 1948 (1961). Isoln from the ripe fruits of *Ligustrum lucidum* and *L. japonicum* Thunb, *Oleaceae:* Inouye, Nishioka, *Tetra-*

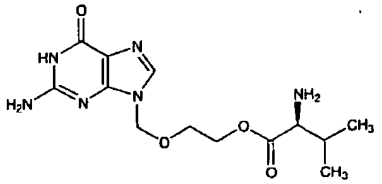
V

9965. Vaccenic Acid. [693-72-1] (11*E*)-11-Octadecenoic acid; *trans*-Δ^{11}-octadecenoic acid. $C_{18}H_{34}O_2$; mol wt 282.46. C 76.54%, H 12.13%, O 11.33%. $CH_3(CH_2)_5CH{=}CH(CH_2)_9COOH$. Found in butterfat and in other animal fats. Growth-promoting factor for rats. Isoln: Bertram, *Biochem. Z.* **197**, 433 (1928). Synthesis: Böesceken, Hoagland, *Rec. Trav. Chim.* **46**, 632 (1927); Ahmad *et al., J. Am. Chem. Soc.* **70**, 3391 (1948). Configuration and ir spectrum: Rao, Daubert, *ibid.* 1102.

Platelets from acetone, mp 43-44°; n_D^{60} 1.4439; n_D^{70} 1.4402. Neutralization equivalent 282.5; iodine no. 89.9.

Methyl ester. $C_{19}H_{36}O_2$. bp_3 172-173°.

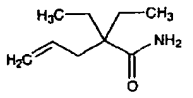
9966. Valacyclovir. [124832-26-4] L-Valine 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]ethyl ester; L-valine ester with 9-[(2-hydroxyethoxy)methyl]guanine; valaciclovir; ValACV. $C_{13}H_{20}N_6O_4$; mol wt 324.33. C 48.14%, H 6.22%, N 25.91%, O 19.73%. L-Valine ester prodrug of acyclovir, *q.v.* Prepn: T. A. Krenitsky *et al.*, **EP 308065**; L. M. Beauchamp, **US 4957924** (1989, 1990 both to Wellcome). Evaluation as prodrug: L. M. Beauchamp *et al., Antiviral Chem. Chemother.* **3**, 157 (1992). Clinical pharmacokinetics: S. Weller *et al., Clin. Pharmacol. Ther.* **54**, 595 (1993). Review of pharmacology and clinical efficacy in herpes virus infections: C. M. Perry, D. Faulds, *Drugs* **52**, 754-772 (1996). Clinical trial to prevent cytomegalovirus disease in renal transplantation: D. Lowance *et al., N. Engl. J. Med.* **340**, 1462 (1999).



Hydrochloride. [124832-27-5] 256U; BW-256U87; BW-256; Valtrex. Crystalline solid, occurs as hydrate. uv max (water): 252.8 nm (ε 8530). Soly in water: 174 mg/ml.

THERAP CAT: Antiviral.

9967. Valdetamide. [512-48-1] 2,2-Diethyl-4-pentenamide; diethylallylacetamide; Novonal. $C_9H_{17}NO$; mol wt 155.24. C 69.63%, H 11.04%, N 9.02%, O 10.31%. Description: Bockmühl, Schaumann, *Deut. Med. Wochenschr.* **54**, 270 (1928). Pharmacokinetics and metabolism: H. Uchleke, M. Brinkschulte-Freitas, *Arch. Pharmacol.* **302**, 11 (1978). TLC determn in urine: E. Klug, P. Toffel, *Arzneimittel-Forsch.* **29**, 1651 (1979).



White powder, mp 75-76°. Sol in 120 parts water; freely sol in alcohol, ether.

THERAP CAT: Sedative, hypnotic.

9968. *n*-Valeraldehyde. [110-62-3] Pentanal; valeral; valeric aldehyde. $C_5H_{10}O$; mol wt 86.13. C 69.72%, H 11.70%, O 18.58%. $CH_3(CH_2)_3CHO$. Prepn: Lieben, Rossi, *Ann.* **159**, 70 (1871); Olsen, **US 2548171** (1951 to GAF); Sisti *et al., J. Org. Chem.* **27**, 279 (1962). Toxicity study: H. F. Smyth *et al., Am. Ind. Hyg. Assoc. J.* **30**, 470 (1969).

Liquid, bp 102-103°, d_4^{20} 0.8095. n_D^{20} 1.3944. Very slightly sol in water; miscible with many organic solvents. LD_{50} orally in rats: 5.66 ml/kg (Smyth).

Caution: Potential symptoms of overexposure are irritation of eyes, skin, nose, throat. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 326.

USE: In flavoring compds, resin chemistry, rubber accelerators.

9969. Valerian. Dried rhizome and roots of *Valeriana officinalis* L., *Valerianaceae. Habit.* Europe, Northern Asia; naturalized in eastern U.S. *Constit.* Volatile oil (−1%); valerine (valerianin) and chatinine (alkaloids); valeric, formic and malic acids; tannin, resin.

Component of *Valerbé*.

THERAP CAT: Sedative.

9970. Valeric Acid, Normal. [109-52-4] Pentanoic acid; valerianic acid; propylacetic acid. $C_5H_{10}O_2$; mol wt 102.13. C 58.80%, H 9.87%, O 31.33%. $CH_3(CH_2)_3COOH$. Obtained by decompn of *n*-propylmalonic acid: Fürth, *Monatsh.* **9**, 308 (1888); from *n*-butyl chloride: Gilman, Kirby, *Org. Syn.* **coll. vol. I**, 363 (2nd ed., 1941). Industrial synthesis by oxidation of amyl alcohol or by fermentation processes. Toxicity study: L. Orö, A. Wretlind, *Acta Pharmacol. Toxicol.* **18**, 141 (1961).

Colorless liquid; unpleasant odor; d_4^{20} 0.939; mp −34.5°; bp 186-187°; bp_{23} 96°; n_D^{20} 1.4086. Sol in 30 parts water; freely sol in alcohol, ether. LD_{50} i.v. in mice: 1290 ±53 mg/kg (Orö, Wretlind).

Ethyl ester. Ethyl *n*-valerate. $C_7H_{14}O_2$. Liquid. d_4^{20} 0.877. bp 145-146°. n_D^{20} 1.3732. Insol in water. Misc with alcohol, ether.

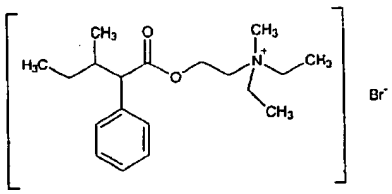
USE: Intermediate in perfumery.

9971. Valeronitrile. [110-59-8] Pentanenitrile; 1-butyl cyanide; 1-cyanobutane. C_5H_9N; mol wt 83.13. C 72.24%, H 10.91%, N 16.85%. $CH_3(CH_2)_3CN$. Prepn: A. Lieben, A. Rossi, *Ann.* **158**, 137 (1871); W. Kantlehner *et al., ibid.* **1980**, 389; H. G. Thomas, H. D. Greyn, *Synthesis* **1990**, 129. Acute toxicity and metabolism: H. Tanii, K. Hashimoto, *Arch. Toxicol.* **55**, 47 (1984). Comparative toxicity of aliphatic nitriles: M. A. Wallig *et al., Food Chem. Toxicol.* **26**, 149 (1988).

bp_{15} 45-47°. $bp_{739.3}$ 140.4°. bp 141°. d^0 0.8164. n_D^{20} 1.3962. Log P (*n*-octanol/water): 0.94. LD_{50} orally in male mice: 2.297 mmol/kg (Tanii).

USE: Solvent.

9972. Valethamate Bromide. [90-22-2] *N,N*-Diethyl-*N*-methyl-2-[(3-methyl-1-oxo-2-phenylpentyl)oxy]ethanaminium bromide; 3-methyl-2-phenylvaleric acid diethyl(3-hydroxyethyl)methylammonium bromide ester; 2-phenyl-3-methylvaleric acid β-(diethylamino)ethyl ester bromomethylate; 3-methyl-2-phenylvaleric acid 2-diethylaminoethyl ester methyl bromide; 2-diethylaminoethyl 2-phenyl-3-methylvalerate methyl bromide; diethyl(2-hydroxyethyl)methylammonium 3-methyl-2-phenylvalerate bromide; Resitan; Epidosin. $C_{19}H_{32}BrNO_2$; mol wt 386.37. C 59.06%, H 8.35%, Br 20.68%, N 3.63%, O 8.28%. Anticholinergic. Prepn: Stühmer, Funke, **DE 969245**; **DE 971136**; **DE 1112989** (all 1958 to Kali-Chemie); Martin, Habicht, **DE 1091124**; **US 2987517** (1960, 1961 both to Cilag-Chemie).



Crystals from ethanol + ether or acetone, mp 100-101°. Freely sol in water, very sol in alcohol. Practically insol in ether. Aq solns are stable to storage; 0.6% ampuled solns showed no loss after one year at room temp.

THERAP CAT: Antispasmodic.

9973. Valganciclovir. [175865-60-8] L-Valine 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl ester; 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)-methoxy]-3-hydroxypropanyl-L-valinate. $C_{14}H_{22}N_6O_5$; mol wt 354.36. C 47.45%, H 6.26%, N 23.72%, O 22.58%. Valine ester prodrug of ganciclovir, *q.v.* Prepn: J. J. Nestor *et al.*, **EP 694547**; *eidem*, **US 6083953** (1996, 2000 both to Hoffmann-La

Figure 2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
human	K	Q	F	T	K	C	E	L	S	Q	L	L	K	D	I	D	G	Y	G	G	I	A	L	P	E	L
bovine	E	Q	L	T	K	C	E	V	F	R	D	L	K	D	L	K	G	Y	G	G	V	S	L	P	E	W

	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
human	I	C	T	M	F	H	T	S	G	Y	D	T	Q	A	I	V	E	N	N	E	S	T	E	Y	G	L
bovine	V	C	T	T	F	H	T	S	G	Y	D	T	Q	A	I	V	Q	N	N	D	S	T	E	Y	G	L

	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78
human	F	Q	I	S	N	K	L	W	C	K	S	S	Q	V	P	Q	S	R	N	I	C	D	I	S	C	D
bovine	F	Q	I	N	N	K	I	W	C	K	D	D	Q	N	P	H	S	S	N	I	C	N	I	S	C	D

	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104
human	K	F	L	D	D	D	I	T	D	D	I	M	C	A	K	K	I	L	D	I	K	G	I	D	Y	W
bovine	K	F	L	D	D	D	L	T	D	D	I	M	C	V	K	K	I	L	D	K	V	G	I	N	Y	W

	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123
human	L	A	H	K	A	L	C	T	E	K	L	E	Q	W	L	C	E	K	L
bovine	L	A	H	K	A	L	C	S	E	K	L	D	Q	W	L	C	E	K	L